

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To: ARLES A. TAYLOR
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NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing (day/month/year)	25 MAR 2009
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Applicant's or agent's file reference 1242/90 PCT	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US 09/32826	International filing date (day/month/year) 02 February 2009 (02.02.2009)
Applicant VANDERBILT UNIVERSITY	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: +41 22 740 14 35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90b*is*.1 and 90b*is*.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the PCT Applicant's Guide, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young
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Form PCT/ISA/220 (January 2004)

DOCKET DATES: 5/25/09 - ART 19
ASSIGNED ATT: AAT/CPD/CEL
FILE NO. 1242/90 PCT
DOCKETED BY: CAS DATE: 3/27/09
PIDS RUE 6/25/09 in 1242/90/2

VJW
4-1-09

(See notes on accompanying sheet)

MAR 27 2009

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 1242/90 PCT	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 09/32826	International filing date (day/month/year) 02 February 2009 (02.02.2009)	(Earliest) Priority Date (day/month/year) 31 January 2008 (31.01.2008)
Applicant VANDERBILT UNIVERSITY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 7 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed.
☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (see Box No. II).

3. ☐ Unity of invention is lacking (see Box No. III).

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. 1
☒ as suggested by the applicant.
☐ as selected by this Authority, because the applicant failed to suggest a figure.
☐ as selected by this Authority, because this figure better characterizes the invention.
- b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/32826

A. CLASSIFICATION OF SUBJECT MATTER

IPC(B) - A61K 31/00, A61K 31/47 (2009.01)

USPC - 424/608, 514/509, 514/44, 514/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

USPC- 424/608, 514/509, 514/44, 514/21

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 424/608, 514/509, 514/44, 514/21 (text search-see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Search terms: nitric oxide, citrulline, subarachnoid hemorrhage, plasma citrulline, vasospasm, trauma

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---	US 6,358,536 B1 (Thomas) 19 March 2002 (19.03.2002), col 1, ln 21-26, col 2, ln 42-45, col 2, ln 53, col 3, ln 12-13, col 7, ln 4, col 9, ln 1, col 13, ln 42-45, col 14, ln 19-22	1-4, 7-13
Y	US 2001/0056068 A1 (Chwalisz et al.) 27 December 2001 (27.12.2001), para [0034], [0064], [0124]; claim 21	5, 6, 14, 15
Y	US 2007/0184554 A1 (Teuscher et al.) 09 August 2007 (09.08.2007), para [0005], [0012], [0084]	5, 6, 14-18
		16-18

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"I" Inter document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

16 March 2009 (16.03.2009)

Date of mailing of the international search report

25 MAR 2009

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
ARLES A. TAYLOR
JENKINS, WILSON, TAYLOR & HUNT, P.A.
SUITE 1200, UNIVERSITY TOWER
3100 TOWER BOULEVARD
DURHAM, NC 27707

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference 1242/90 PCT		Date of mailing (day/month/year) 25 MAR 2009	
International application No. PCT/US 09/32826		FOR FURTHER ACTION See paragraph 2 below	
International filing date (day/month/year) 02 February 2009 (02.02.2009)	Priority date (day/month/year) 31 January 2008 (31.01.2008)		
International Patent Classification (IPC) or both national classification and IPC IPC(B) - A61 K 31/00, A61 K 31/47 (2009.01) USPC - 424/608, 514/509, 514/44, 514/21			
Applicant VANDERBILT UNIVERSITY			

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Date of completion of this opinion 16 March 2009 (16.03.2009)	Authorized officer: Lee W. Young <small>PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774</small>
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Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 09/32826

Box No. 1 Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:
- ☒ the international application in the language in which it was filed.
- ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a)).
3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of:
- a. type of material
- ☐ a sequence listing
- ☐ table(s) related to the sequence listing
- b. format of material
- ☐ on paper
- ☐ in electronic form
- c. time of filing/furnishing
- ☐ contained in the international application as filed
- ☐ filed together with the international application in electronic form
- ☐ furnished subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 09/32826

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	5, 6, 14-18	YES
	Claims	1-4, 7-13	NO
Inventive step (IS)	Claims	none	YES
	Claims	1-18	NO
Industrial applicability (IA)	Claims	1-18	YES
	Claims	none	NO

2. Citations and explanations:

Claims 1-4 and 7-13 lack novelty under PCT Article 33(2) as being anticipated by US 6,358,536 B1 (Thomas).

Regarding claim 1, Thomas discloses a method of treating a complication associated with aneurysmal subarachnoid hemorrhage (SAH) (col 3, in 12-13), the method comprising administering an effective amount of a nitric oxide precursor to a subject in need thereof (col 2, in 42-45).

Regarding claim 2, Thomas further discloses wherein the subject has suffered trauma that results in SAH (col 1, in 21-26).

Regarding claim 7, Thomas discloses a method of treating vasospasm (col 7, in 4), the method comprising administering an effective amount of a nitric oxide precursor to a subject in need thereof (col 2, in 42-45).

Regarding claim 8, Thomas further discloses wherein the vasospasm is associated with aneurysmal subarachnoid hemorrhage in the subject (col 3, in 12-13).

Regarding claim 9, Thomas discloses that the subject has suffered trauma that results in vasospasm (col 1, in 21-28).

Regarding claim 10, Thomas further discloses wherein the vasospasm is associated with atherosclerosis in the subject (col 1, in 24-25).

Regarding claim 11, Thomas further discloses wherein the atherosclerosis is associated with coronary arterial disease (col 2, in 53).

Regarding claims 3 and 12, Thomas further discloses wherein the nitric oxide precursor comprises a precursor that generates citrulline in vivo (col 8, in 1, arginine = precursor of citrulline), a pharmaceutically acceptable salt thereof, and combinations thereof (col 13, in 42-45).

Regarding claims 4 and 13, Thomas further discloses wherein the administering is intravenously or orally (col 14, in 18-22).

Claims 5, 6, 14, and 15 lack inventive step under PCT Article 33(3) as being obvious over Thomas in view of US 2001/0059068 A1 to Chwalisz et al. (hereinafter "Chwalisz").

Regarding claims 5 and 14, Thomas does not specifically disclose that the nitric oxide precursor is administered in a dose ranging from about 100 mg to about 30,000 mg. However, Chwalisz discloses a method to treat vasospasm (para [0034]) comprising 200 mg to 10 g citrulline (para [0084]). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to incorporate the dosage of citrulline as disclosed by Chwalisz to the composition of treating vasospasm with nitric oxide precursor of Thomas, providing a composition comprising 100 mg to 30,000 mg of citrulline for the treatment of vasospasm, since both Thomas and Chwalisz teach methods in applying nitric oxide precursors to treat vasospasm.

Regarding claims 6 and 15, Chwalisz further discloses wherein the nitric oxide precursor is administered in a dose ranging from about 250 mg to about 1,000 mg (para [0064]).

Claims 16-18 lack inventive step under PCT Article 33(3) as being obvious over Chwalisz in view of US 2007/0184554 A1 to Teuscher et al. (hereinafter "Teuscher").

Regarding claim 16, Chwalisz discloses a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an amount of citrulline effective to raise plasma arginine level to treat a complication associated with vasospasm in a subject (para [0034] and claim 21). Chwalisz does not specifically disclose said composition comprising determining plasma citrulline level. However, Teuscher discloses that circulating citrulline, a precursor of arginine, could be used as a biomarker for intestinal disorders (para [0005] and [0012]) by comparing plasma citrulline levels in a subject to be treated to that observed in a subject not suffering from a complication associated with intestinal disorders (para [0084]). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to apply the determination of the circulating citrulline level as disclosed by Teuscher to the method of treating vasospasm to effectively raise circulating arginine level of Chwalisz, since citrulline is a precursor of arginine.

-----continued in Supplemental Box-----

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 09/32826

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Box V2. Citations and explanation

Regarding claim 17, Teuscher further discloses wherein the amount of citrulline effective to raise plasma citrulline level in a subject to at least 5 $\mu\text{mol/liter}$, optionally at least 10 $\mu\text{mol/liter}$, optionally at least 20 $\mu\text{mol/liter}$, optionally at least 25 $\mu\text{mol/liter}$, and optionally about 37 $\mu\text{mol/liter}$ (para [0084]).

Regarding claim 18, Chwalisz further discloses wherein the pharmaceutical composition is adapted for oral administration (para [0124]).

Claims 1-18 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.